INTRODUCTION

In this study the efficacy of the dual PPAR-α/γ agonist Saroglitazar in preventing progression of early NASH F0 to more advanced NASH with fibrosis was investigated in Sanyal Biotechnology's DIAMOND™ mouse model. It has previously been demonstrated that the pure PPAR-α agonist, Pioglitazone, attenuates some measures of NASH and metabolic syndrome in this mouse model, which develops all of the symptoms of human metabolic syndrome and NASH when fed a Western Diet 1,2. Saroglitazar has previously improved liver function and fibrosis in other rodent models of NASH such as CCL4-induced fibrosis model and the choline-deficient high-fat diet model 3. We hypothesized that administration of Saroglitazar may also prevent progression of NASH in the DIAMOND™ model.

AIMS

(1) To determine if Saroglitazar administration could prevent progression of NASH.
(2) To compare the efficacy of Saroglitazar with benchmarks Pioglitazone and positive and negative natural history controls.

METHOD

8 week old DIAMOND™ mice (10-12 per group) were weight randomized and placed on either normal chow/normal water (NC/NW) or Western Diet/sugar water (WD/SW) for 12 weeks. At 12 weeks on diet the WD/SW groups were fed high fat Western Diet/High Sugar Water (WD/HSW) to progress to full metabolic syndrome with NASH. Daily oral gavage of Saroglitazar (4 mg/kg/day), Pioglitazone (30 mg/kg/day) and vehicle (water) began at 8 week old DIAMOND™ mice for 12 weeks. At 12 weeks on diet the WD/SW controls and positive WD/SW controls did progress. The pathogenesis of NASH and metabolic syndrome/diabetes have been shown to be mechanistic drivers in common. This study demonstrated that Saroglitazar inhibits steatosis, inflammation, ballooning, and fibrosis in addition to lowering body weight, serum LFTs and lipids. Saroglitazar ameliorated NASH development and progression in addition to improving measures of insulin resistance and diabetes. Saroglitazar met the primary study endpoint of preventing NASH progression in the DIAMOND™ mouse model, and the secondary endpoint of outperforming the efficacy of benchmark Pioglitazone in the DIAMOND™ mouse model.

CONCLUSIONS

The pathogenesis of NASH and metabolic syndrome/diabetes have mechanistic drivers in common. This study demonstrated that Saroglitazar inhibits steatosis, inflammation, ballooning, and fibrosis in addition to lowering body weight, serum LFTs and lipids. Saroglitazar ameliorated NASH development and progression in addition to improving measures of insulin resistance and diabetes. Saroglitazar met the primary study endpoint of preventing NASH progression in the DIAMOND™ mouse model, and the secondary endpoint of outperforming the efficacy of benchmark Pioglitazone in the DIAMOND™ mouse model.

ACKNOWLEDGEMENTS

We thank Myriam Clements of EVMS for her histology services, and Ryan Huyck of EVMS for his technical assistance.

REFERENCES


CONTACT INFORMATION

Dr. Rebecca Caffrey, Sanyal Biotechnology, rebecca@sanyalbio.com